REMARKS/ARGUMENTS

I. Status of the Claims.

Claims 1-22, 35, 37-39 and 66-85 are pending. Claims 16 and 18-22 have been withdrawn from examination by the Examiner as being directed to non-elected subject matter. Claims 1-15, 17, 35, 37-39 and 66-85 are under examination.

By this Response, no new matter has been added to the application.

II. Response to Claim Rejections

Pending claim rejections are summarized and addressed as follows.

(i) Double Patenting Rejection

Claims 1-15, 35, 37-39 and 66-85 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting over certain claims of co-pending application no. 10/719,553 ("the '553 application"). Applicants confirm that the '553 application has not issued as a patent. Accordingly, it is requested that the instant rejection be held in abeyance.

(ii) Rejections Under 35 U.S.C. §112, second paragraph (indefiniteness)

Claims 1-15, 17, 35, 37-39 and 66-85 were rejected for alleged indefiniteness. The Examiner's position is that the limitations of "being 'a mutant allergen of a naturally occurring allergen" and "known homologous protein" are unclear. The Examiner states that the scope of the claims would be changeable as more wild-type allergen sequences are identified. The rejection is traversed.

The standard for definiteness is whether "those skilled in the art would understand what is claimed when the claim is read in light of the specification." *Orthokinetics, Inc., v.*

Safety Travel Chairs, Inc., 806 F.2d 1565, 1576 (Fed. Cir. 1986). Here, the Examiner has failed to provide a supportable basis for concluding that one of ordinary skill in the art would not understand what is claimed when the claims are read in light of the specification. It is noted at the outset that the claims call for a "recombinant mutant allergen of a naturally occurring allergen." The meaning of "naturally occurring allergen" is self-evident, i.e., an allergen that is obtained from the wild. A recombinant mutant allergen of a naturally occurring allergen is therefore simply a naturally-occurring allergen that has been mutated. Contrary to the Examiner's position, the phrase "recombinant mutant allergen of a naturally occurring allergen" is clear on its face. The phrase "known homologous protein" is similarly clear on its face. Additionally, the Examiner's position concerning the possibility that the scope of the claims may change as more wild-type allergen are identified is not believed to be well taken. Compliance with section 112 is measured against the knowledge of skill in the art at the time the application was filed. The possible discovery of additional wild-type allergens thus does not make the claims indefinite.

Lastly, the response to the Examiner's query concerning whether "naturally occurring sequences" comprising particular amino acids at positions listed on page 31, line 25 to page 32, line 2 of the specification is straight forward. Naturally occurring allergens are not encompassed by the instant claims.

For the reasons set forth above, the claims are not indefinite. Reconsideration of the claims and withdrawal of the rejections under 35 U.S.C. §112, second paragraph is requested.

(iii) Rejection Under 35 U.S.C. §112, first paragraph (written description)

Claims 1-15, 17, 35, 37-39 and 66-85 remain rejected for alleged failure to comply with the written description requirement. The Examiner maintains the specification fails to provide adequate written description for the functional limitations set out in the claims and fails to adequately describe compositions comprising a plurality of recombinant mutant allergens or pharmaceutical compositions comprising recombinant mutant allergens. The rejection is respectfully traversed. Applicants' previously-filed amendments and responses have outlined in

detail the reasons why the specification provides written description for the claimed invention. *See*, e.g., responses filed October 31, 2007, April 7, 2009 and August 4, 2010.

The rejected claims are directed to recombinant mutant allergens of a naturally occurring allergen selected from the group consisting of Fagales group 1 allergens, Vespidae antigen 5 allergens, house dust mite group 1 allergens, house dust mite group 2 allergens and grass group 5 allergens. *See* claim 1. The claims are thus directed to recombinant mutant allergens derived from Fagales group 1 allergens, Vespidae antigen 5 allergens, house dust mite group 1 allergens, house dust mite group 2 allergens and grass group 5 allergens and comprising at least four mutations, which each reduce the specific IgE binding capability of the mutated allergen as compared to the IgE binding capability of the naturally occurring allergen, each of said at least four mutations being a substitution of one surface-exposed amino acid residue with another residue, which does not occur in the same position in the amino acid sequence of any known homologous protein within the taxonomic species from which said naturally occurring allergen originates, each of said at least four mutations being spaced from each other by at least 15 Å, and comprising at least one circular surface region with a area of 800 $Å^2$ that comprises no mutation.

The specification provides adequate written description for the claimed recombinant mutant allergens. The written description requirement requires that the specification provide disclosure that allows one of ordinary skill in the art of the invention to "recognize that [the inventor] invented what is claimed." *Lockwood v. American Airlines, Inc.,* 107 F.3d 1565, 1572 (Fed. Cir. 1997); *see also Vas-Cath Inc. v. Mahurkar,* 935 F.2d 1555, 1563-64 (Fed. Cir. 1991) (Applicant "must convey with reasonable clarity to those skilled in the art that ... he or she was in possession *of the invention.*") (emphasis in original). The written description requirement "ensure[s] that the scope of the right to exclude, as set forth in the claims, does not overreach the scope of the inventor's contribution to the field of art as detailed in the patent specification." *Reiffin v. Microsoft Corp.,* 214 F.3d 1342, 1354 (Fed. Cir. 2000). The written description requirement is met by providing sufficient structural, physical and/or functional properties that describe a genus and/or a sufficient members of genus that show the

inventors were in possession of the claimed invention. *Regents of the University of California v. Eli Lilly & Co.,* 119 F.3d 1559, 1567-68 (Fed. Cir. 1997). Functional language may provide adequate written description "if in the knowledge of the art the disclosed function is sufficiently correlated with a particular, known structure." *Amgen Inc. v. Hoechst Marion Roussel, Inc.,* 314 F.3d 1313, 1332 (Fed. Cir. 2003) *citing Enzo Biochem, Inc. v. Gen-Probe, Inc.,* 296 F.3d 1316, 1324 (Fed. Cir. 2002).

The instant application sets forth the claimed invention in sufficient detail to show that Applicants were in possession of the claimed invention. Hence, the specification discloses that "the invention is based on the recognition that a mutated allergen having IgE binding reducing mutations in multiple be cell epitopes, and at least one intact epitope" would reduce crosslinking IgE, and thus the allergenicity of the mutant allergens, while preserving at least one epitope to raise an IgG response. Specification at page 18, lines 29-36. The specification discloses that the recombinant mutant allergens are produced by making substitutions of at least four surfaced-exposed, conserved amino acids that are spaced from each other by at least 15 Å, while preserving at least one circular surface region of 800 $Å^2$. Specification at, e.g., page 19, line 21-page 20, line 1. The spacing of the at least four mutations ensures that they are in separate clusters of epitopes. Specification at page 20, lines 14-17. In addition to the at least four mutations spaced at least 15 Å from each other, the recombinant mutant allergens may further comprise additional mutations ("secondary mutations") that further reduce IgE binding. Specification at page 24, line 27 through page 25, line 8. These additional mutations are also placed such that a 800 $Å^2$ area free of mutations is preserved. Specification at page 25, lines 2-3. The specification further sets forth detailed "Criteria for substitution." Specification at page 36-38.

The specification further gives detailed analysis on the structural features of Bet v 1, Der p 2, Ves v 5, Der p 1, and Phl p 5 and related proteins that further show possession of the claimed invention. Thus, the specification discloses 57 amino acids of Bet v 1 that are highly solvent exposed and conserved (page 68), 54 amino acids of Der p 2 that are highly solvent

exposed and conserved (page 72), 88 amino acids of Ves v 5 that are highly solvent exposed and conserved (page 76) and sets forth 12 Der p 2 mutants (pages 97-98), 11 Der p 1 mutants (pages 105-106), 14 Phl p 5 mutants (pages 114-115). The detailed description of amino acids to be mutated and the combinations of mutants demonstrate that the inventors had possession of the claimed invention as it relates to Bet v 1, Ves v 5, Der p 1, Der p 2, and Phl p 5. Moreover, as disclosed in the specification, Bet v 1, Ves v 5, Der p 1, Der p 2, and Phl p 5 are highly homologous to allergens Fagales group 1 allergens, Vespidae antigen 5 allergens, house dust mite group 1 allergens, house dust mite group 2 allergens and grass group 5 allergens, respectively. See specification at page 81, lines 1-15 (67 sequences homologous to Bet v 1 within the order Fagales), page 58 and Fig. 10 A (Vespula Ag 5s about 90% identical), Fig. 35 A and B (sequence alignment of Der p 1 and other house dust mite group 1 allergens), Fig. 32 (sequence of Der p 2 with other house dust mite group 2 allergens), and Fig. 38 A-D (sequence alignment of Phl p 5 with other grass group 5 allergens). One of ordinary skill in the art would understand that the high degree of sequence identity among the members of the respective allergen families recited in the claims means that description of recombinant mutant allergens for a single member of the family provides written description for recombinant mutant allergens of any allergen within the same family. Thus, the specification provides written description for the recombinant mutant allergens called for in the subsisting claims.

In setting forth the instant rejection, the Examiner has cited *Eli Lilly*, *supra*. The nature of the instant invention and the disclosure of the instant specification, however, are very different from *Eli Lilly*. In *Eli Lilly*, the Federal Circuit held that the disclosure of the sequence of a rat insulin cDNA did not provide adequate written description for the insulin cDNA sequence of every vertebrate. *Eli Lilly* at 1566-67. In *Eli Lilly*, however, the specification failed to provide any features that described the claimed vertebrate insulin cDNA. The Court found that the claimed cDNA were described solely by their function or how to obtain them. The instant case is inapposite to *Eli Lilly*. In *Eli Lilly* the claims were directed to unknown cDNA sequences. The instant claims, by contrast, are drawn to mutant allergens that are derived by making substitutions in a family of allergens, i.e., Fagales group 1 allergens, Vespidae antigen 5

allergens, house dust mite group 1 allergens, house dust mite group 2 allergens and grass group 5 allergens, with closely related sequences. In *Eli Lilly*, no structural features were provided that correlated with the function of the claimed vertebrate insulin cDNA. In the instant case, the specification provides that substituted amino acids are those amino acids that are conserved, solvent accessible amino acids that are spaced at least 15 Å from each other and which are each outside a circular area of 800 $Å^2$ on the surface of the allergen and goes on to list particular amino acids to choose among to make the claimed recombinant mutant allergens.

Nor does the decision of the Board of Patent Appeals and Interferences in *ex parte Kubin* (83 USPQ2d 1410 (BPAI 2007[1])) support a finding that the instant specification fails to provide adequate written description for the pending claims. In *Kubin*, the Board upheld the rejection of a claim directed to isolated polynucleotides encoding polypeptides that (1) "are at least 80% identical to amino acids 22-221 of SEQ ID NO: 2" (i.e., the amino acid sequence for the extracellular domain of the protein natural killer cell activation inducing ligand ("NAIL") lacking the NAIL signal sequence) and (2) which bind to the glycoprotein CD 48. *Id.* at 1417. The specification in *Kubin* disclosed the sequence of two nucleic acids within the scope of the claim and three fusion proteins whose nucleic acid sequences would fall within the scope of the claim. *Id.* None of these sequences varied amino acids 22-221 of SEQ ID NO: 2. *Id.*

The Board in *Kubin* found that the Applicant had failed to describe what domains of within amino acids 22-221 of SEQ ID NO: 2 correlated with the function of binding CD 48, and thus the Applicant had not described which NAIL amino acids could be varied and still maintain CD 48 binding. *Id.* Citing *Eli Lilly*, the Board found that in the absence of a structure-function correlation, the claim merely defined the invention by function, which was not sufficient to satisfy the written description requirement.

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[1] The Court of Appeals for the Federal Circuit affirmed the Board's decision in Kubin on the grounds that the claims were obvious over the prior art. *In re Kubin,* 561 F.3d 1351, 1358-61 (Fed. Cir. 2009). The Federal Circuit, however, declined to address the question of whether the claims in Kubin were properly rejected for failure to comply with the written description requirement. *Id.* at 1361.

Kubin is distinguished from the instant case for much the same reasons as *Eli Lilly*. In *Kubin*, the Applicant failed to provide any features of amino acids 22-221 of SEQ ID NO: 2 that correlated with binding to CD 48. As set forth above, the instant specification, in contrast, allows one of ordinary skill in the art to identify amino acids Fagales group 1 allergens, Vespidae antigen 5 allergens, house dust mite group 1 allergens, house dust mite group 2 allergens and grass group 5 allergens. Furthermore, whereas in *Kubin* the Applicant failed to disclose any polynucleotides encoding NAIL protein that varied in amino acids 22-221, the instant applications identifies numerous amino acid for substitution in Fagales group 1 allergens, Vespidae antigen 5 allergens, house dust mite group 1 allergens, house dust mite group 2 allergens and grass group 5 allergens, and further sets forth examples of combinations of mutants, whereas the Applicant in *Kubin* failed to provide any working examples of polynucleotides encoding a polypeptide at least 80% identical to amino acids 22-221 of SEQ ID NO: 2 and which bind CD 48.

In short, as with *Eli Lilly*, the Applicant in *Kubin* failed to provide any structural features that correlated with the function of the polypeptide called for in the claim, whereas the instant specification sets out the features, including specific amino acids, of Fagales group 1 allergens, Vespidae antigen 5 allergens, house dust mite group 1 allergens, house dust mite group 2 allergens and grass group 5 allergens that are called for in the claims and which allow one of ordinary skill in the mutant art to make the claimed recombinant allergens. Thus, the basis of the Board's decision in *Kubin* does not apply to the instant claims.

The structure of Bet v 1 was known at the time the application was filed and Bet v 1 allergens are highly conserved. There is no rule that the Applicants provide description of the precise mutant amino acids in the claimed recombinant Bet v 1 mutants. *Falkner v. Inglis,* 448 F.3d 1357, 1366 (Fed. Cir. 2006). Applicants are entitled to "flexibility" in how they claim their invention. *Univ. of Rochester v. G.D. Searle & Co., Inc.,* 358 F.3d 916, 927-928 (Fed. Cir. 2004). In *Ariad v. Eli Lilly*, the Federal Circuit reiterated, "[written description] doctrine never created a heightened requirement to provide a nucleotide-by-nucleotide recitation of the entire

genus of claimed genetic material; it has always expressly permitted the disclosure of structural features common to the members of the genus." *Ariad Pharmaceuticals, Inc. v. Eli Lilly and Co.,* cv 2008-1248, Fed. Cir., *en banc,* decided March 22, 2010, slip op at 26, *citations omitted.* Here, when measured against the known, conserved structure of Bet v 1 allergens and the high level of skill in the art concerning B-cell epitopes, the claims tell one of ordinary skill in the art where mutations are placed in the claimed recombinant allergens. The claims thus describe the claimed invention and do not "merely [draw] a fence around the outer limits of a purported genus." *Id.* at 21.

In short, the specification teaches that the starting point for the claimed recombinant mutant allergens are known proteins, i.e., a naturally occurring allergens, and further gives clear teachings on how to use such starting material to arrive at the claimed invention. The state of the art, moreover, is high. One of ordinary skill in the art would thus immediately envision that the claimed recombinant mutant allergens bearing the mutations made according the teachings of the specification would largely retain the structure and antigenicity of wild-type allergens from which they are derived. The Examiner has failed to adduce any evidence to the contrary.

Additionally, the Examiner's statements t "Applicants have no way of knowing how to modify as yet undiscovered allergens that may differ from known allergens in ways that cannot be contemplated" and there "is no way to know what is or is not an allergen encompassed by the scope of the claims given the information disclosed in the specification" are not well taken. First the possibility that, notwithstanding the conserved structure of antigenicity among allergens in the same family, "undiscovered allergens that may differ from known allergens in ways that cannot be contemplated" is pure conjecture on the basis of the Examiner is therefore of little probative value. Contrary to the Examiner's assertion, the specification teaches precisely how to modify as yet undiscovered naturally-occurring allergens to arrive at the claimed invention. Lastly, the Examiner's statements concerning the scope of the claims blur the requirements for indefiniteness, enablement, and written description. These are additional reasons why the written description rejection should be withdrawn.

Lastly, the Examiner's comments concerning the difference among the allergens disclosed in Smith are not well taken. As set forth above, "naturally-occurring" allergens are not encompassed by the claims. Thus, Smith does not provide evidence that the specification fails to provide written description for the claimed invention.

For at least the reasons set forth above, the specification provides sufficient written description to show Applicants were in possession of the full scope of the claimed invention when the application was filed. Reconsideration of the claims and withdrawal of all rejections thereof for lack of written description is requested.

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III. Conclusion.

This application is believed to be in condition for allowance.

Respectfully submitted,

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